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Case report

Amantadine-related corneal edema and endothelial cell loss: Four case reports

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ABSTRACT

Amantadine is widely used in treating influenza A, hepatitis, Parkinson's disease, and fatigue in multiple sclerosis. In the past, only a few case reports have demonstrated that amantadine is associated with corneal edema, endothelial dysfunction, and other corneal comorbidity. We herein present four cases with reversible corneal edema and endothelial loss after taking amantadine, including two cases with delayed presentation of corneal edema after use of amantadine for 18 months and 12 months.

1. Introduction

Amantadine was originally utilized as an antiviral medication for influenza A or hepatitis.[1] It was later introduced in the treatment of Parkinson's disease, associated drug-induced dyskinesia, and even fatigue of multiple sclerosis patients.[1,2] Corneal edema associated with amantadine therapy has been noticed during the past 4 decades, with few cases having been reported in the literature.[3–11] Here, we report four cases of corneal edema and endothelial cell loss caused by oral intake of amantadine.

2. Case reports

2.1. Case 1

An 80-year-old female with a history of dementia and bipolar disease consulted our clinic due to bilateral blurred vision. She had undergone bilateral cataract surgery 6 months previously uneventfully. At the first presentation in our clinic, her best-corrected visual acuities (BCVAs) of the right and left eyes were 0.3 and 0.05, respectively. Slit-lamp examination revealed bilateral corneal stromal edema (Fig. 1). The anterior chamber was silent, both the intraocular lenses were in good positions, and the intraocular pressure was normal. Optical coherence tomography (OCT) showed the corneal thickness of the right and left eyes to be 650 μm and 731 μm, respectively. In the absence of infectious or inflammatory signs, pseudophakic bullous keratopathy or virus infection-related corneal edema was suspected. Topical 3% NaCl and Alphagan were given for relieving corneal edema. Two weeks later, corneal edema in both eyes decreased slightly, to 625 μm and 730 μm, respectively.

Her medication was then carefully reviewed, which was as follows: triazolam 0.25 mg/day, amantadine 200 mg/day, quetiapine 200 mg/day, and bupropion 150 mg/day. Among these drugs, amantadine was prescribed 3 weeks prior to the initiation of ocular symptoms. Considering the possible side effect of amantadine to induce the corneal edema, we suggested discontinuation of amantadine use. However, this suggestion was disapproved by her psychiatrist due to the clinical demand for her psychological symptoms. Two months later, the patient's corneal edema and Descemet's membrane wrinkling deteriorated. To rule out virus infection, polymerase chain reaction of aqueous humor was performed for the detection of cytomegalovirus and herpes simplex virus, and the results were negative for both viruses. After further discussion with the psychiatrist, amantadine was eventually discontinued. The corneal edema subsided gradually. Four weeks after the cessation of amantadine, BCVAs of both eyes improved to 0.6. Corneal thickness of the right and left eyes decreased to 484 μm

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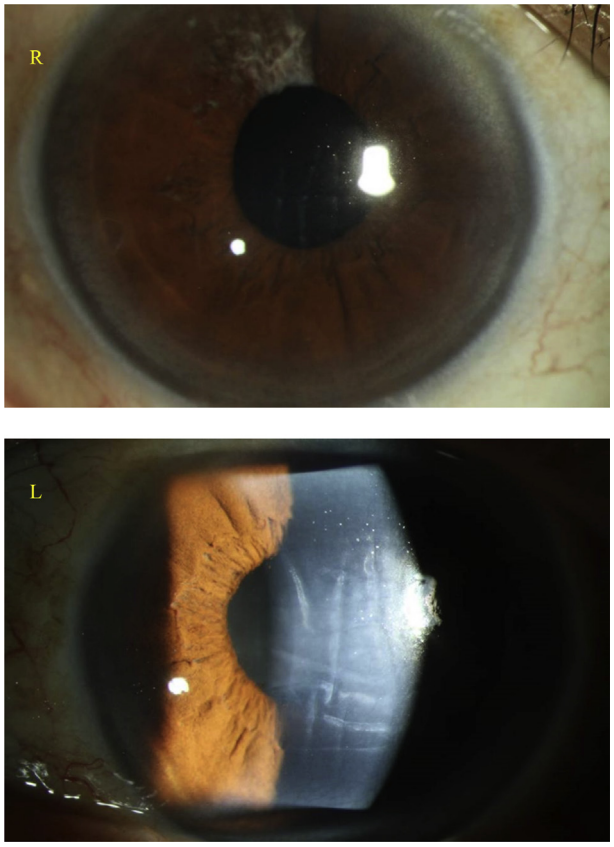

Fig. 1. Bilateral corneal edema with a corneal thickness of 650 μm in the right eye and 731 μm in the left eye (Case 1).

and 504 μm, respectively. Specular microscopy showed that corneal endothelium counts were 1828 cell/mm^2 and 1927 cell/mm^2, respectively. Hexagonicity of endothelial cells decreased in the left eye, with a large amount of cells having irregular shapes (Fig. 2). The last follow-up was 3 months after cessation of amantadine, and the BCVA remained at 0.6 in both eyes.

2.2. Case 2

A 53-year-old female with Parkinson's disease and major depression suffered from painless blurred vision, with visual hallucination for 3 weeks. She had undergone bilateral cataract surgery 2 years previously. When she visited our clinic, the BCVA was 0.1 in both eyes. Slit-lamp examination showed bilateral corneal stromal edema in the central one-third (Fig. 3). In the absence of an anterior chamber reaction or vitreous opacity, 1% prednisolone and 3% NaCl were prescribed for treating the corneal edema. However, no subjective visual improvement was noticed after 2 weeks of treatment.

We reviewed her medication and found that she was taking levodopa, pramipexole, and amantadine for Parkinson's disease from 6 weeks prior to the onset of ocular symptoms; additionally, she took quetiapine for depression. Without an obvious cause of corneal edema, amantadine-related corneal edema was suspected. Amantadine was thus discontinued with approval from her neurologist. Two weeks later, her BCVA of the right eye remained at 0.1, but that of the left eye improved to 0.4. OCT showed the corneal thickness of the right and left eyes to be 739 μm and 697 μm, respectively. One percent prednisolone was then tapered gradually. Four weeks later, her BCVA improved to 0.7 in both eyes, and the corneal thickness decreased to 560 μm and 565 μm, respectively.

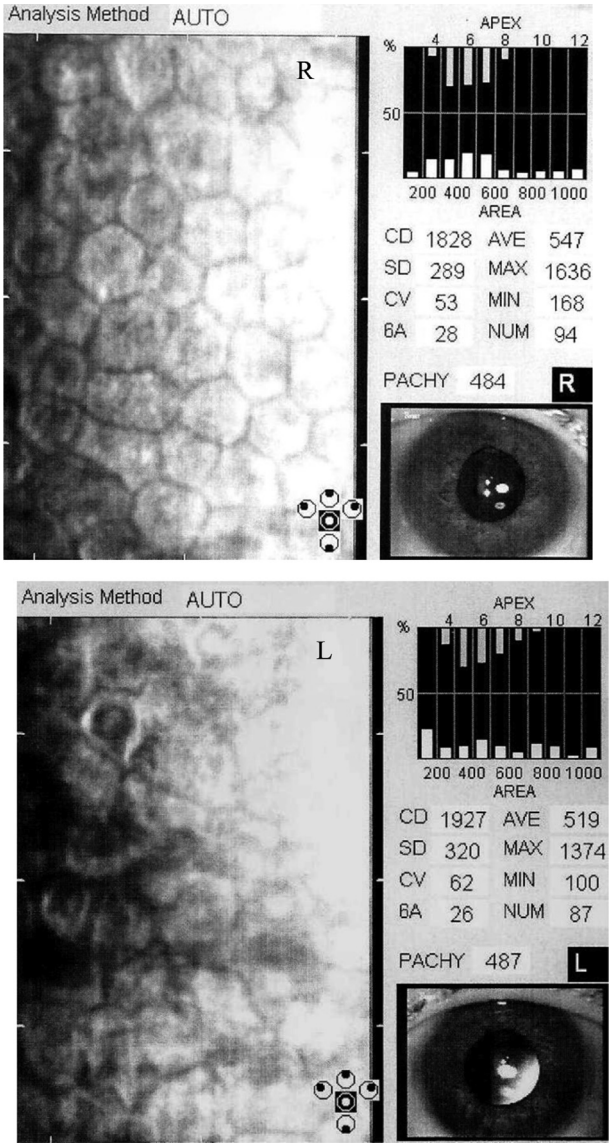

Fig. 2. Decreased endothelial cell count with increased polymorphism and polymegathism (Case 1).

2.3. Case 3

A 72-year-old female with Parkinson's disease complained of gradual bilateral blurring of vision for 1 month. She denied ocular trauma or surgery history. No other ocular symptoms such as tearing, pain, and foreign body sensation were observed. On the first ophthalmologic visit, the BCVAs of the right and left eyes were 0.04 and 0.06, respectively. The autorefractor failed to show the refraction data. During slit-lamp examination, bilateral symmetric corneal edema in the central two-thirds and Descemet's membrane folding were found. No guttata was observed, and the anterior chamber was quiet. Grade 2 cataracts were noted in both eyes. There was no conjunctival congestion or chemosis. Fundus was veiled due to corneal edema even after mydriasis, but there was normal retinal red reflex and the optic discs were not pale. Pachymetry and specular microscopic endothelial count failed due to marked corneal edema. Intraocular pressure and light reflex were normal. Sonography showed no vitreous opacity or retinal detachment. After reviewing her medication history, it was found

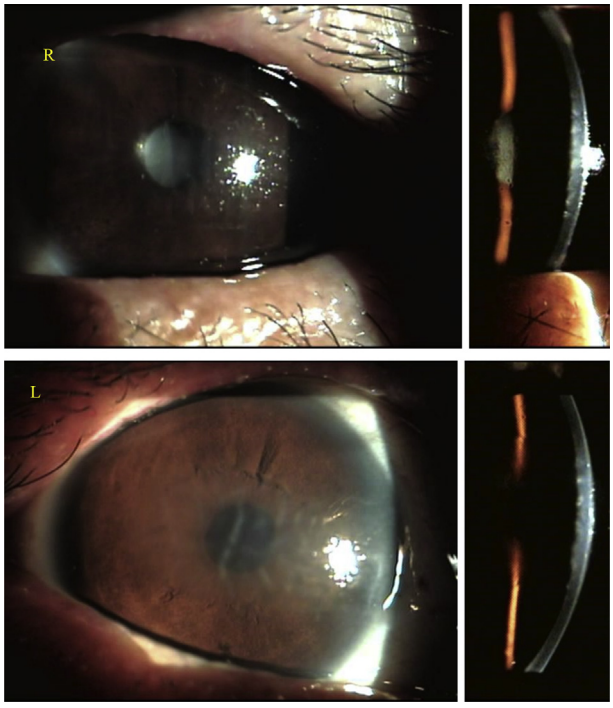

Fig. 3. With marked corneal edema, the best corrected visual acuity of both eyes was 0.1 (Case 2).

that she had been taking oral amantadine for 18 months for Parkinson's disease. In addition, visual hallucination was noticed by her family. Under the suspicion of amantadine-induced corneal edema, amantadine was discontinued after discussion with her neurologist. Topical 0.1% dexamethasone was prescribed.

The corneal edema resolved completely 4 weeks after cessation of amantadine. The BCVAs of the right and left eyes improved to 0.5 and 0.7, respectively. Specular microscopy showed that endothelial cell densities were only 1149/mm^2 and 1256/mm^2, respectively. Final corneal thicknesses were measured as 566 μm and 552 μm, respectively.

2.4. Case 4

A 66-year-old male consulted our clinic with the chief complaint of floater for 1 month and blurred vision for 4 days accompanied with visual hallucination. Slit-lamp examination revealed central corneal edema with Descemet's membrane folding. The anterior chamber was silent without cell or keratic precipitate. The BCVA of the right eye was 0.2 under a correction of +8.0 D with a history of amblyopia, and that of the left eye was 0.4. The patient was taking various medications for depression and Parkinson's disease, prescribed by different hospitals. Corneal thicknesses of the right and left eyes were 834 μm and 851 μm, respectively. Specular microscopy failed due to swollen cornea. Although the patient did not bring his drug list with him, amantadine-induced corneal keratopathy was suspected on the basis of our previous experience. Three percent NaCl and 0.1% fluorometholone were prescribed for symptomatic relief. The patient was instructed to check his medicine at home and stop amantadine if there were any being taken; later, the use of amantadine 200 mg/day for 12 months was confirmed and ceased with the approval of his neurologist. One month later, the BCVAs were improved to 0.5 and 0.8, respectively, for the right and left eyes. Corneal thicknesses decreased to 593 μm and 595 μm, and endothelial densities were 1730/mm^2 and 1704/mm^2, respectively.

3. Discussion

Amantadine is an antiviral drug originally used as a prophylactic and for the treatment of influenza A and hepatitis.[1] People have found it to be useful as an antiparkinsonian agent, although the mechanism is not well understood.[1] Besides, it has also been utilized in treating fatigue of multiple sclerosis patients.[2] For treating viral diseases, amantadine is used for a short period only. For Parkinson's disease or multiple sclerosis, it may be used for months to years.

Some systemic side effects of amantadine have been noted, including cardiac dysfunction, psychiatric illness, seizure, peripheral edema, dry mouth, and nasal irritation.[1] Ocular side effects include superficial punctate keratitis,[1,5–7] punctate subepithelial opacities, epithelial edema,[10] and stromal edema.[8–11] The side-effect occurrence rate of amantadine has been reported to be around 5–20%.[1] Nevertheless, symptoms are generally mild and transient, and seen mainly with dosages higher than 200 mg/day.[1] Ophthalmologic adverse events of amantadine have been reported since the 1970s, which include transient and sudden visual deterioration resulting from bilateral corneal edema after weeks of amantadine therapy. The corneal edema usually resolved after cessation of amantadine, but has been known to recur after the drug was resumed.[5–8]

As reported in previous studies, corneal edema has occurred weeks, months, and even years after amantadine therapy, with most of them taking place within 2 years.[5–8] In our first two cases, the onset of corneal edema was 3–4 weeks after taking amantadine. However, it occurred 18 months and 12 months after the institution of amantadine in our third and fourth cases, respectively. Moreover, there are four reported cases in the literature demonstrating the occurrence of corneal edema following a prolonged period (up to 3–8 years) after starting amantadine therapy.[4,9,11] The large variability in the corneal edema onset time after administration of amantadine may be related to the different endothelial cell densities at baseline in different patients. Besides, despite the mechanism of amantadine-induced corneal edema not being clear, idiosyncratic hypersensitivity has been suggested by some authors,[10] which might explain the large variability in the onset time of corneal edema after taking amantadine. Corneal edema of our cases improved within 4–6 weeks after cessation of amantadine, which is consistent with previous reports.

In our cases, the final corneal endothelial cell density decreased significantly despite recovery of corneal edema. Although the baseline specular endothelial count data were unavailable due to severe corneal edema, the final endothelial cell density was obviously lower than that of an age-comparable population. Because amantadine-related corneal edema was found to be associated with endothelial dysfunction and cell loss, corneal edema may be irreversible if the endothelial loss is significant. Jeng et al[10] reported a case with bilateral corneal edema after taking amantadine. Penetrating keratoplasty was performed in one eye due to severe corneal edema. Because amantadine was not ceased, the endothelial cell loss maintained progression in both eyes, resulting in graft edema. After cessation of amantadine, the graft edema subsided, and penetrating keratoplasty was performed in the fellow eye to treat irreversible corneal edema. Due to the possibility of irreversible corneal edema after amantadine use, care must be taken when the patients are at high risk with factors such as old age, low corneal endothelial count, corneal dystrophy, or grafted cornea.

All our cases presented with bilateral progressive painless visual deterioration due to corneal stromal edema with Descemet's folds after an uneventful period of amantadine therapy. Anterior chambers were all silent, without keratic precipitates or cells. Although ocular side effects of amantadine includes superficial punctate

keratitis and epithelial edema,[5–7] to our knowledge, stromal edema are the most often reported manifestation of amantadine-related keratopathy. Hence, in patients with bilateral progressive painless corneal stromal edema without any clue to the disease entity, careful medication review is an easy but crucial step prior to invasive diagnostic procedures.

In elderly patients with Parkinson's disease, depression, or other physical illness, visual deterioration is easily overlooked due to poor verbal expression. It should be kept in mind that amantadine can cause corneal edema, and regular ophthalmological follow-up is important in these patients.

In conclusion, amantadine can cause corneal edema after weeks, months, or even years of its administration. Patients most often present with bilateral corneal stromal edema without anterior chamber reaction. Corneal edema usually subsides after cessation of the drug, with irreversible corneal endothelial cell loss. It should be used carefully in patients with a low corneal endothelial count. Besides, ophthalmic consultation is suggested prior to and during amantadine therapy. Careful medication review is crucial in patients with an unknown etiology of corneal edema.

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